GRANISETRON HYDROCHLORIDE- granisetron hydrochloride injection, solution
Yung Shin Pharmaceutical Inc. Co., Ltd.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Granisetron Hydrochloride Injection USP safely and effectively. See full prescribing information for Granisetron Hydrochloride Injection USP.

Granisetron Hydrochloride Injection USP, for intravenous use

Initial U.S. Approval: 1993

RECENT MAJOR CHANGES

Warnings and Precautions (5.4)	08/2014

INDICATIONS AND USAGE

Granisetron Hydrochloride Injection USP is a serotonin-3 (5-HT_3) receptor antagonist indicated for:

- Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. (1)
- Prevention and treatment of postoperative nausea and vomiting in adults. (1)

DOSAGE AND ADMINISTRATION

Prevention of chemotherapy-induced nausea and vomiting (2.1):

- Recommended dosage is 10 mcg/kg intravenously within 30 minutes before initiation of chemotherapy
- Pediatric patients (2 to 16 years): Recommended dosage is 10 mcg/kg

Prevention of postoperative nausea and vomiting (2.2):

- Recommended dosage is 1 mg, undiluted, administered intravenously over 30 seconds, before anesthetic induction or immediately before reversal of anesthesia.

Treatment of postoperative nausea and vomiting (2.2):

- Recommended dosage is 1 mg, undiluted, administered intravenously over 30 seconds

DOSAGE FORMS AND STRENGTHS

- Injection 0.1 mg(base)/mL. (3)

CONTRAINDICATIONS

- Hypersensitivity to granisetron or to any of its components. (4)

WARNINGS AND PRECAUTIONS

- Granisetron hydrochloride does not stimulate gastric or intestinal peristalsis and should not be used instead of nasogastric suction. (5.1)
- QT prolongation has been reported with granisetron hydrochloride. Use with caution in patients with pre-existing arrhythmias or cardiac conduction disorders. (5.2)
- Hypersensitivity reactions, such as anaphylaxis, shortness of breath, hypotension, and urticaria, may occur in patients with known hypersensitivity to other selective 5-HT_3 receptor antagonists. (5.3)
- Serotonin syndrome has been reported with granisetron products, alone but particularly with concomitant use of serotonergic drugs. (5.4)

ADVERSE REACTIONS

Most common adverse reactions:

- Chemotherapy-induced nausea and vomiting (≥3%): Headache, and constipation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Carlsbad Technology, Inc. at 1-855-397-9777; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Granisetron hydrochloride injection has been administered safely with benzodiazepines, neuroleptics, and anti-ulcer medications. (7)
- Does not appear to interact with emetogenic cancer chemotherapies. (7)
- Inducers or inhibitors of CYP450 enzymes may change the clearance and therefore the half-life of granisetron. (7)
- Coadministration of granisetron hydrochloride with drugs known to prolong the QT interval and/or are arrhythmogenic may result in clinical consequences. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if clearly needed. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric use: Safety and efficacy in pediatric patients have not been established for use in postoperative nausea and vomiting. (8.4)
- Geriatric use: No differences in responses between the elderly and younger patients were observed in reported clinical experience. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Granisetron Hydrochloride Injection USP is a serotonin-3 (5-HT3) receptor antagonist indicated for:

- The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high- dose cisplatin.
- The prevention and treatment of postoperative nausea and vomiting in adults. As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided during the postoperative period, Granisetron Hydrochloride Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Chemotherapy-Induced Nausea and Vomiting

Adult Patients

The recommended dosage for granisetron hydrochloride injection USP is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.

Infusion Preparation
Granisetron hydrochloride injection USP may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes.

Stability
Intravenous infusion of granisetron hydrochloride injection USP should be prepared at the time of administration. However, granisetron hydrochloride injection USP has been shown to be stable for at least 24 hours when diluted in 0.9% Sodium Chloride or 5% Dextrose and stored at room temperature under normal lighting conditions.
As a general precaution, granisetron hydrochloride injection USP should not be mixed in solution with other drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Pediatric Patients
The recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg [see Clinical Studies (14)]. Pediatric patients under 2 years of age have not been studied.

2.2 Prevention and Treatment of Postoperative Nausea and Vomiting

Adult Patients

The recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of Granisetron Hydrochloride Injection, undiluted, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia.

The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1 mg of Granisetron Hydrochloride Injection, undiluted, administered intravenously over 30 seconds.

3 DOSAGE FORMS AND STRENGTHS

Single-Use Vials for Injection: 0.1 mg(base)/mL

4 CONTRAINDICATIONS

Granisetron hydrochloride injection is contraindicated in patients with known hypersensitivity (eg. anaphylaxis, shortness of breath, hypotension, urticaria) to the drug or to any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Gastric or Intestinal Peristalsis

Granisetron hydrochloride is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of granisetron hydrochloride in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

5.2 Cardiovascular Events

An adequate QT assessment has not been conducted, but QT prolongation has been reported with granisetron hydrochloride. Therefore, granisetron hydrochloride should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

5.4 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastronintestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of granisetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue granisetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if granisetron is used concomitantly with other serotonergic drugs [*see Drug Interactions (7), Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

QT prolongation has been reported with granisetron hydrochloride *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in patients.

Chemotherapy-Induced Nausea and Vomiting

The following have been reported during controlled clinical trials or in the routine management of

patients. The percentage figures are based on clinical trial experience only. Table 1 gives the comparative frequencies of the two most commonly reported adverse reactions (≥3%) in patients receiving granisetron hydrochloride injection, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following granisetron hydrochloride injection administration. Reactions were generally recorded over seven days post-granisetron hydrochloride injection administration.

Table 1 Principal Adverse Reactions in Clinical Trials Single-Day Chemotherapy

	Percent of Patients With Reaction	
	Granisetron Hydrochloride Injection 40 mcg/kg (n=1268)	**Comparator* (n=422)**
Headache	14%	6%
Constipation	3%	3%

*Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

Additional adverse events reported in clinical trials were asthenia, somnolence and diarrhea.

In over 3,000 patients receiving granisetron hydrochloride injection (2 to 160 mcg/kg) in single-day and multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than those adverse reactions listed in Table 1, were observed; attribution of many of these events to granisetron hydrochloride is uncertain.

Hepatic: In comparative trials, mainly with cisplatin regimens, elevations of AST and ALT (>2 times the upper limit of normal) following administration of granisetron hydrochloride injection occurred in 2.8% and 3.3% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2.1%; ALT: 2.4%).

Cardiovascular: Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including non-sustained tachycardia, and ECG abnormalities have been observed rarely.

Central Nervous System: Agitation, anxiety, CNS stimulation and insomnia were seen in less than 2% of patients. Extrapyramidal syndrome occurred rarely and only in the presence of other drugs associated with this syndrome.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (eg, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: Fever (3%), taste disorder (2%), skin rashes (1%). In multiple-day comparative studies, fever occurred more frequently with granisetron hydrochloride injection (8.6%) than with comparative drugs (3.4%, $P<0.014$), which usually included dexamethasone.

Postoperative Nausea and Vomiting

The adverse reactions listed in Table 2 were reported in 2% of adults receiving Granisetron Hydrochloride Injection 1 mg during controlled clinical trials.

Table 2 Adverse Reactions in Controlled Clinical Trials in Postoperative Nausea and Vomiting (Reported in 2% of Adults Receiving Granisetron Hydrochloride Injection 1 mg)

	Percent of Patients With Reaction	
	Granisetron Hydrochloride Injection 1 mg (n=267)	**Placebo (n=266)**

Pain	10.1	8.3
Headache	8.6	7.1
Fever	7.9	4.5
Abdominal Pain	6.0	6.0
Hepatic Enzymes Increased	5.6	4.1
Dizziness	4.1	3.4
Diarrhea	3.4	1.1
Flatulence	3.0	3.0
Dyspepsia	3.0	1.9
Oliguria	2.2	1.5
Coughing	2.2	1.1

Additional adverse events reported in clinical trials were constipation, anemia, insomnia, bradycardia, leukocytosis, anxiety, hypotension, infection, hypertension, and urinary tract infection.

In a clinical study conducted in Japan, the types of adverse events differed notably from those reported above in Table 2. The adverse events in the Japanese study that occurred in 2% of patients and were more frequent with Granisetron Hydrochloride Injection 1 mg than with placebo were: fever (56% to 50%), sputum increased (2.7% to 1.7%), and dermatitis (2.7% to 0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of granisetron hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to granisetron hydrochloride exposure.

QT prolongation has been reported with granisetron hydrochloride *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*.

7 DRUG INTERACTIONS

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system *in vitro*. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs; however, in humans, granisetron hydrochloride injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Granisetron hydrochloride injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron hydrochloride *in vitro*.

In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of granisetron hydrochloride. However, the clinical significance of *in vivo* pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous granisetron hydrochloride. The clinical significance of this change is not known.

QT prolongation has been reported with granisetron hydrochloride. Use of granisetron hydrochloride in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic may result in clinical consequences.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other

serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m^2/day, 146 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 3 mg/kg/day (35.4 mg/m^2/day, 96 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when granisetron hydrochloride injection is administered to a nursing woman.

8.4 Pediatric Use

Chemotherapy-Induced Nausea and Vomiting

[See Dosage and Administration (2)] for use in chemotherapy-induced nausea and vomiting in pediatric patients 2 to 16 years of age. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Postoperative Nausea and Vomiting

Safety and efficacy have not been established in pediatric patients for the prevention of postoperative nausea and vomiting (PONV). Granisetron has been evaluated in a pediatric patient clinical trial for use in the prevention of PONV. Due to the lack of efficacy and the QT prolongation observed in this trial, use of granisetron for the prevention of PONV in children is not recommended. The trial was a prospective, multicenter, randomized, doubleblind, parallel-group trial that evaluated 157 children aged 2 to 16 years who were undergoing elective surgery for tonsillectomy or adenotonsillectomy. The purpose of the trial was to assess two dose levels (20 mcg/kg and 40 mcg/kg) of intravenous granisetron in the prevention of PONV. There was no active comparator or placebo. The primary endpoint was total control of nausea and vomiting (defined as no nausea, vomiting/retching, or use of rescue medication) in the 24 hours following surgery. Efficacy was not established due to lack of a dose response.

The trial also included standard 12 lead ECGs performed pre-dose and after the induction of anesthesia. ECGs were repeated at the end of surgery after the administration of granisetron and just prior to reversal of anesthesia. QT prolongation was seen at both dose levels. Five patients in this trial experienced an increase of ≥ 60 msec in QTcF. In addition, there were two patients whose QTcF was ≥ 500 msec. Interpretation of the QTcF prolongation was confounded by multiple factors, including the use of concomitant medication and the lack of either a placebo or active control. A thorough QT trial in adults has not been performed.

Other adverse events that occurred in the study included: vomiting (5 to 8%), post-procedural hemorrhage (3 to 5%), and dehydration (0 to 5%).

Pediatric patients under 2 years of age have not been studied.

8.5 Geriatric Use

During chemotherapy clinical trials, 713 patients 65 years of age or older received granisetron hydrochloride injection. The safety and effectiveness were similar in patients of various ages.

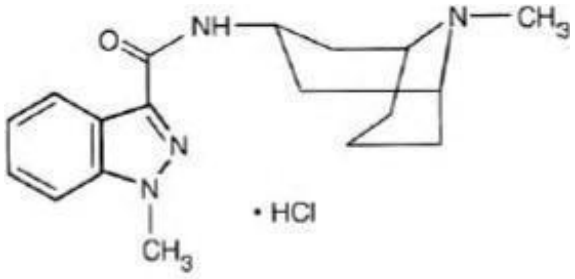
During postoperative nausea and vomiting clinical trials, 168 patients 65 years of age or older, of which 47 were 75 years of age or older, received granisetron hydrochloride injection. Clinical studies of granisetron hydrochloride injection did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

There is no specific antidote for granisetron hydrochloride injection overdosage. In case of overdosage, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride injection has been reported without symptoms or only the occurrence of a slight headache.

11 DESCRIPTION

Granisetron hydrochloride injection USP is a serotonin-3 (5-HT_3) receptor antagonist. Chemically it is *endo*-N-(9-methyl-9- azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O$•HCl, while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. Granisetron hydrochloride injection USP is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration. Granisetron hydrochloride injection USP, 0.1 mg(base)/mL is available in a 1 mL single-use vial.

0.1 mg/mL: Each 1 mL contains 0.112 mg granisetron hydrochloride equivalent to granisetron, 0.1 mg; sodium chloride, 9 mg; citric acid monohydrate, 2 mg; water for injection, USP/EP q.s.; sodium hydroxide and hydrochloric acid, as pH adjusters. Contains no preservative. The solution's pH ranges from 4 to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1; 5-HT_{1A}; 5-$HT_{1B/C}$; 5-HT_2; for alpha$_1$-, alpha$_2$- or beta-adrenoreceptors; for dopamine-D_2; or for histamine-H_1; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT_3 type are located peripherally on vagal nerve terminals and centrally in

the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to 5-HT_3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Granisetron hydrochloride injection exhibited no effect on oro-cecal transit time in normal volunteers given a single intravenous infusion of 50 mcg/kg or 200 mcg/kg. Single and multiple oral doses slowed colonic transit in normal volunteers.

12.3 Pharmacokinetics

Chemotherapy-Induced Nausea and Vomiting

In adult cancer patients undergoing chemotherapy and in volunteers, mean pharmacokinetic data obtained from an infusion of a single 40 mcg/kg dose of granisetron hydrochloride injection are shown in Table 3.

Table 3 Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single Intravenous 40 mcg/kg Dose of Granisetron Hydrochloride Injection

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Cancer Patients				
Mean	63.8*	8.95*	0.38*	3.07*
Range	18.0 to 176	0.90 to 31.1	0.14 to 1.54	0.85 to 10.4
Volunteers				
21 to 42 years				
Mean	64.3†	4.91†	0.79†	3.04†
Range	11.2 to 182	0.88 to 15.2	0.20 to 2.56	1.68 to 6.13
65 to 81 years				
Mean	57.0†	7.69†	0.44†	3.97†
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

*5-minute infusion.

†3-minute infusion.

Distribution

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. *In vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT_3 receptor antagonist activity.

Elimination

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 12% of the administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine, and 34% in the feces.

Subpopulations

Gender

There was high inter- and intra-subject variability noted in these studies. No difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

Elderly

The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of granisetron hydrochloride injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly patients (see Table 3).

Pediatric Patients

A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single 40 mcg/kg intravenous dose of granisetron hydrochloride injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are similar in pediatric and adult cancer patients.

Renal Failure Patients

Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of granisetron hydrochloride injection.

Hepatically Impaired Patients

A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients, dosage adjustment in patients with hepatic functional impairment is not necessary.

Postoperative Nausea and Vomiting

In adult patients (age range, 18 to 64 years) recovering from elective surgery and receiving general balanced anesthesia, mean pharmacokinetic data obtained from a single 1 mg dose of Granisetron Hydrochloride Injection administered intravenously over 30 seconds are shown in Table 4.

Table 4 Pharmacokinetic Parameters in 16 Adult Surgical Patients Following a Single Intravenous 1 mg Dose of Granisetron Hydrochloride Injection

	Terminal Phase Plasma Half-Life (h)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Mean	8.63	0.28	2.42
Range	1.77 to 17.73	0.07 to 0.71	0.71 to 4.13

The pharmacokinetics of granisetron in patients undergoing surgery were similar to those seen in cancer patients undergoing chemotherapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during

week 59 due to toxicity. For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 16, 81 and 405 times the recommended clinical dose (0.37 mg/m^2, iv) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m^2/day, 81 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 405 times the recommended human dose based on body surface area).

No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m^2/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 81 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m^2/day, 1622 times the recommended human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, granisetron hydrochloride injection should be prescribed only at the dose and for the indication recommended *[see Indications and Usage (1) and Dosage and Administration (2)]*.

Granisetron was not mutagenic in an *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m^2/day, 97 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Chemotherapy-Induced Nausea and Vomiting

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy

In a double-blind, placebo-controlled study in 28 cancer patients, granisetron hydrochloride injection, administered as a single intravenous infusion of 40 mcg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy (see Table 5).

Table 5 Prevention of Chemotherapy-Induced Nausea and Vomiting Single-Day Cisplatin Therapy [a]

	Granisetron Hydrochloride Injection	Placebo	P-Value
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response [b]	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

[a] Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m2 in the granisetron hydrochloride injection group and 80 mg/m2 in the placebo group.

[b] No vomiting and no moderate or severe nausea.

Granisetron hydrochloride injection was also evaluated in a randomized dose response study of cancer patients receiving cisplatin ≥75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs, and vinca alkaloids. Granisetron hydrochloride injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly superior to 10 mcg/kg (see Table 6).

Table 6 Prevention of Chemotherapy-Induced Nausea and Vomiting Single-Day High-Dose Cisplatin Therapy [a]

	Granisetron Hydrochloride Injection (mcg/kg)			**P-Value (vs. 2 mcg/kg)**	
	2	**10**	**40**	**10**	**40**
Number of Patients	52	52	53		
Response Over 24 Hours					
Complete Response [b]	31%	62%	68%	<0.002	<0.001
No Vomiting	38%	65%	74%	<0.001	<0.001
No More Than Mild Nausea	58%	75%	79%	NS	0.007

[a] Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m2.
[b] No vomiting and no moderate or severe nausea.

Granisetron hydrochloride injection was also evaluated in a double-blind, randomized dose response study of 353 patients stratified for high (≥80 to 120 mg/m^2) or low (50 to 79 mg/m^2) cisplatin dose. Response rates of patients for both cisplatin strata are given in Table 7.

Table 7 Prevention of Chemotherapy-Induced Nausea and Vomiting Single-Day High-Dose and Low-Dose Cisplatin Therapy [a]

	Granisetron Hydrochloride Injection (mcg/kg)				**P-Value (vs. 5 mcg/kg)**		
	5	**10**	**20**	**40**	**10**	**20**	**40**
High-Dose Cisplatin							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response [b]	18%	41%	40%	47%	0.018	0.025	0.004
No Vomiting	28%	47%	44%	53%	NS	NS	0.016
No Nausea	15%	35%	38%	43%	0.036	0.019	0.005
Low-Dose Cisplatin							
Number of Patients	42	41	40	46			
Response Over 24 Hours							
Complete Response [b]	29%	56%	58%	41%	0.012	0.009	NS

No Vomiting	36%	63%	65%	43%	0.012	0.008	NS
No Nausea	29%	56%	38%	33%	0.012	NS	NS

[a] Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m2 for low and high strata.
[b] No vomiting and no use of rescue antiemetic.

For both the low and high cisplatin strata, the 10, 20, and 40 mcg/kg doses were more effective than the 5 mcg/kg dose in preventing nausea and vomiting within 24 hours of chemotherapy administration. The 10 mcg/kg dose was at least as effective as the higher doses.

Moderately Emetogenic Chemotherapy Granisetron hydrochloride injection, 40 mcg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. Granisetron hydrochloride injection was superior to the chlorpromazine regimen in preventing nausea and vomiting (see Table 8).

Table 8 Prevention of Chemotherapy-Induced Nausea and Vomiting— Single-Day Moderately Emetogenic Chemotherapy

	Granisetron Hydrochloride Injection	Chlorpromazine [a]	P-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response [b]	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

[a] Patients also received dexamethasone, 12 mg.
[b] No vomiting and no moderate or severe nausea.

In other studies of moderately emetogenic chemotherapy, no significant difference in efficacy was found between granisetron hydrochloride doses of 40 mcg/kg and 160 mcg/kg.

Repeat-Cycle Chemotherapy

In an uncontrolled trial, 512 cancer patients received granisetron hydrochloride injection, 40 mcg/kg, prophylactically, for two cycles of chemotherapy, 224 patients received it for at least four cycles, and 108 patients received it for at least six cycles. Granisetron hydrochloride injection efficacy remained relatively constant over the first six repeat cycles, with complete response rates (no vomiting and no moderate or severe nausea in 24 hours) of 60% to 69%. No patients were studied for more than 15 cycles.

Pediatric Studies

A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer patients (age 2 to 16 years) to granisetron hydrochloride injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin 60 mg/m^2, cytarabine 3 g/m^2, cyclophosphamide 1 g/m^2 or nitrogen mustard 6 mg/m^2 (see Table 9).

Table 9 Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

	Granisetron Hydrochloride Injection Dose (mcg/kg)		
	10	**20**	**40**
Number of Patients	29	26	25
Median Number of Vomiting Episodes	2	3	1

Complete Response Over 24 Hours [a]	21%	31%	32%

[a] No vomiting and no moderate or severe nausea.

A second pediatric study compared granisetron hydrochloride injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide 3 g/m^2/day for two or three days. Granisetron hydrochloride injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of granisetron hydrochloride injection patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine regimen. The median number of vomiting episodes with granisetron hydrochloride injection was 1.5; with chlorpromazine it was 7.

14.2 Postoperative Nausea and Vomiting

Prevention of Postoperative Nausea and Vomiting

The efficacy of Granisetron Hydrochloride Injection for prevention of postoperative nausea and vomiting was evaluated in 868 patients, of which 833 were women, 35 men, 484 Caucasians, 348 Asians, 18 Blacks, 18 Other, with 61 patients 65 years or older. Granisetron Hydrochloride Injection was evaluated in two randomized, double-blind, placebo-controlled studies in patients who underwent elective gynecological surgery or cholecystectomy and received general anesthesia. Patients received a single intravenous dose of Granisetron Hydrochloride Injection (0.1 mg, 1 mg or 3 mg) or placebo either 5 minutes before induction of anesthesia or immediately before reversal of anesthesia. The primary endpoint was the proportion of patients with no vomiting for 24 hours after surgery. Episodes of nausea and vomiting and use of rescue antiemetic therapy were recorded for 24 hours after surgery. In both studies, Granisetron Hydrochloride Injection (1 mg) was more effective than placebo in preventing postoperative nausea and vomiting (see Table 10). No additional benefit was seen in patients who received the 3 mg dose.

Table 10 Prevention of Postoperative Nausea and Vomiting in Adult Patients

Study and Efficacy Endpoint	Placebo	Granisetron Hydrochloride Injection 0.1mg	Granisetron Hydrochloride Injection 1mg	Granisetron Hydrochloride Injection 3mg
Study 1				
Number of Patients	**133**	**132**	**134**	**128**
No Vomiting				
0 to 24 hours	34%	45%	63%**	62%**
No Nausea				
0 to 24 hours	22%	28%	50%**	42%**
No Nausea or Vomiting				
0 to 24 hours	18%	27%	49%**	42%**
No Use of Rescue Antiemetic Therapy				
0 to 24 hours	60%	67%	75%	77%
Study 2				
Number of Patients	**117**	-	**110**	**114**
No Vomiting				
0 to 24 hours	56%	-	77%**	75%*
No Nausea				
0 to 24 hours	37%	-	59%	56%

*P<0.05

**P<0.001 versus placebo

Note: No Vomiting = no vomiting and no use of rescue antiemetic therapy; No Nausea = no nausea and no use of rescue antiemetic therapy

Gender/Race

There were too few male and Black patients to adequately assess differences in effect in either population.

Treatment of Postoperative Nausea and Vomiting

The efficacy of Granisetron Hydrochloride Injection for treatment of postoperative nausea and vomiting was evaluated in 844 patients, of which 731 were women, 113 men, 777 Caucasians, 6 Asians, 41 Blacks, 20 Other, with 107 patients 65 years or older. Granisetron Hydrochloride Injection was evaluated in two randomized, double-blind, placebo-controlled studies of adult surgical patients who received general anesthesia with no prophylactic antiemetic agent, and who experienced nausea or vomiting within 4 hours postoperatively. Patients received a single intravenous dose of Granisetron Hydrochloride Injection (0.1 mg, 1 mg or 3 mg) or placebo after experiencing postoperative nausea or vomiting. Episodes of nausea and vomiting and use of rescue antiemetic therapy were recorded for 24 hours after administration of study medication. Granisetron Hydrochloride Injection was more effective than placebo in treating postoperative nausea and vomiting (see Table 11). No additional benefit was seen in patients who received the 3 mg dose.

Table 11 Treatment of Postoperative Nausea and Vomiting in Adult Patients

Study and Efficacy Endpoint	**Placebo**	**Granisetron Hydrochloride Injection 0.1mg**	**Granisetron Hydrochloride Injection 1mg**	**Granisetron Hydrochloride Injection 3mg**
Study 3				
Number of Patients	**133**	**128**	**133**	**125**
No Vomiting				
0 to 6 hours	26%	53%***	58%***	60%***
0 to 24 hours	20%	38%***	46%***	49%***
No Nausea				
0 to 6 hours	17%	40%***	41%***	42%***
0 to 24 hours	13%	27%**	30%**	37%***
No Use of Rescue Antiemetic Therapy				
0 to 6 hours	–	–	–	–
0 to 24 hours	33%	51%**	61%***	61%***
Study 4				
Number of Patients (All Patients)	**162**	**163**	–	–
No Vomiting				
0 to 6 hours	20%	32%*	–	–
0 to 24 hours	14%	23%*	–	–
No Nausea				
0 to 6 hours	13%	18%	–	–
0 to 24 hours	9%	14%	–	–
No Nausea or Vomiting				
0 to 6 hours	13%	18%	–	–
0 to 24 hours	9%	14%	–	–
No Use of Rescue				

Antiemetic Therapy 0 to 6 hours 0 to 24 hours	– 24%	– 34%*	– –	– –
Number of Patients (Treated for Vomiting)[1]	**86**	**103**	–	–
No Vomiting 0 to 6 hours 0 to 24 hours	 21% 14%	 27% 20%	 – –	 – –

*P<0.05
**P<0.01
***P<0.001 versus placebo

[1] Protocol Specified Analysis: Patients who had vomiting prior to treatment

Note: No vomiting = no vomiting and no use of rescue antiemetic therapy; No nausea = no nausea and no use of rescue antiemetic therapy

Gender/Race

There were too few male and Black patients to adequately assess differences in effect in either population.

16 HOW SUPPLIED/STORAGE AND HANDLING

Granisetron Hydrochloride Injection USP, 0.1 mg(base)/mL (free base), is supplied in 1 mL Single-Use Vial. CONTAINS NO PRESERVATIVE.

NDC Number	Contents	Package size
NDC 63126-331-15	0.1 mg(base)/mL	5 Single-Use Vials

Store single-use vials at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Discard unused portion for the single-use vials.
Do not freeze. Protect from light. Retain in carton until time of use.

17 PATIENT COUNSELING INFORMATION

Patients should be informed that the most common adverse reactions for the indication of chemotherapy induced nausea and vomiting are headache and constipation (see Table 1).

Patients should be informed that the most common adverse reactions for the indication of postoperative nausea and vomiting are pain, headache, fever, abdominal pain and hepatic enzyme increased (see Table 2).

Patients should be advised of the risk of allergic reactions if they have a prior allergic reaction to a class of antiemetics known as 5- HT_3 receptor antagonists.

Electrocardiogram changes (QT prolongation) have been reported with the use of granisetron hydrochloride. Patients should be cautioned about the use of this drug if they have heart problems or take medications for heart problems.

Advise patients of the possibility of serotonin syndrome with concomitant use of granisetron and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms.

Rev. 12/2016

Manufactured by:

Yung Shin Pharmaceutical Ind. Co., Ltd.

Tachia, Taichung 43769, TAIWAN

Distributed by:

Carlsbad Technology, Inc.

5928 Farnsworth Ct., Carlsbad, CA 92008, USA

Granisetron Hydrochloride Injection USP, 0.1 mg(base)/mL (free base)

5 Single-Use Vials

GRANISETRON HYDROCHLORIDE

granisetron hydrochloride injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63126-331
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GRANISETRON HYDROCHLORIDE (UNII: 318F6L70J8) (GRANISETRON - UNII:WZG3J2MCOL)	GRANISETRON	0.1 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Chloride (UNII: 451W47IQ8X)	
Citric Acid Monohydrate (UNII: 2968PHW8QP)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63126-331-15	5 in 1 BOX	12/01/2020	
1		1 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202647	12/01/2020	

Labeler - Yung Shin Pharmaceutical Inc. Co., Ltd. (656108149)

Registrant - Yung Shin Pharmaceutical Inc. Co., Ltd. (658843289)

Establishment

Name	Address	ID/FEI	Business Operations
Yung Shin Pharmaceutical Inc. Co., Ltd.		658843289	manufacture(63126-331)

Revised: 12/2016 Yung Shin Pharmaceutical Inc. Co., Ltd.